Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372:1898-908. DOI: 10.1056/NEJMoa1411480

SUPPLEMENTARY APPENDIX

PERSONNEL, SITES, FUNDING AND ACKNOWLEGEMENTS

Lead Site - University of Michigan, Ann Arbor, Michigan
Principal Investigator (PI) (Scientific) - Frank W. Moler, MD, MS

Data Coordinating Center (DCC), University of Utah, Salt Lake City, Utah.
Principal Investigator DCC - J. Michael Dean, MD, MBA
Lead Biostatistician - Richard Holubkov, PhD

Outcome Center, Kennedy Krieger Institute, Baltimore, Maryland. Academic affiliation with Johns Hopkins University, School of Medicine
James R. Christensen, MD, Beth S. Slomine, PhD

Executive Committee

F. Moler, MD, MS,	PI (Scientific)	University of Michigan
J. M. Dean, MD, MBA	PI (DCC)	University of Utah
R. Holubkov, PhD	Biostatistician	University of Utah
K. Meert, MD	Critical Care	Wayne State University
J. Hutchison, MD	Critical Care	University of Toronto
V. Nadkarni, MD	Critical Care	University of Pennsylvania
N. Kuppermann, MD, MPH	Emergency Medicine	UC-Davis
S. Shankaran, MD	Neonatology	Wayne State University
F. Silverstein, MD	Neurology	University of Michigan
J. Christensen, MD	Rehabilitation Medicine	Kennedy-Krieger Institute
V. Pemberton, RNC, MS	NHLBI	NIH
C. Nicholson, MD, MS	NICHD, CPCCRN	NIH
T. Singh Weik, DrPH	MCHB EMSC, PECARN	HRSA

Sites and research teams - contributors

We acknowledge the contributions of the following sites and individuals who made the THAPCA-OH Trial possible.

Site principal investigators (PI), Sub-investigators (Sub-I), Clinical research coordinators (CRC), and Research Assistant (RA).

Underline indicates is a coauthor.

The Children's Hospital of Alabama, Birmingham, AL

J. Alten (PI), S. Borasino (Sub-I), C. Pruitt (Sub-I), R. Bush (CRC), K. Hock (CRC), L. Dure (Neurologist), D, Marullo (Psychologist)

Arkansas Children's Hospital, Little Rock, AR

R. Sanders (PI), P. Prodhan (Sub-I), G. Hefley (CRC)

Phoenix Children's Hospital, Phoenix, AZ

H. J. Dalton (PI), S. Buttram (Sub-I), K. Wai (Sub-I), A. La Bell (CRC), C. Bliss (CRC), D. Liss (CRC), A. Ortiz (CRC), C. Downhour (CRC), K. Williams (Neurologist), M. Lavoie (Psychologist), V. Bordes-Edgar (Psychologist)

Diamond Children's Medical Center, Tucson, AZ

A. Theodorou (PI), K. Typpo (Sub-I), C. Wells (CRC), J. Deschenes (CRC), J. Teodori (Neurologist), C. Viscusi (Sub-I), J. Katsanis (Psychologist)

Children's Hospital Los Angeles, Los Angeles, CA

C. Newth (PI), S. Rubin (Sub-I), R. Bart (Sub-I), T, Deakers (Sub-I), A. Ghuman (Sub-I), R. Khemani (Sub-I), B. Markovitz (Sub-I), J. Dicarlo (Sub-I), P. Ross (Sub-I), V. Wang (Sub-I), M. Villa (CRC), F. Fajardo (CRC), J. Kwok (CRC), J. Serrano (CRC), J. Valentine (CRC), J. Terry (CRC), A. Yamakawa (CRC), S. Briones (CRC), S. Cauley (RN), A. Briseno (RN), C. Young (RN), M. Nyc (CRC), T. Rosser (Neurologist), J. Gold (Psychologist), R. Engilman (Psychometrician)

Children's Hospital of Orange County, Orange, CA

A. Schwarz (PI), J. Haykawa (Sub-I), T. Patterson (CRC), O. Vargas-Shiraishi (CRC), A. Galion (Neurologist), P. Armstrong (Psychologist)

Loma Linda University Children's Hospital, Loma Linda, CA

M. Mathur (PI), G. Oei (Sub-I), B. Barcega (Sub-I), J. Newcombe (CRC), A. Pinto (CRC), S. Ashwal (Neurologist), D. Michelson (Neurologist), J. Pivonka-Jones (Neuropsychologist)

Mattel Children's Hospital UCLA, Los Angeles, CA

R. Harrison (PI), R. Kelly (Sub-I), A. Madikians (Sub-I), M. Federman (Sub-I), M. Morgan (Sub-I), A. Yamakawa (CRC), M. Nyc (CRC), S. Briones (CRC), M. Villa (CRC), J. Kwok (CRC), J. Serrano (CRC), J. Valentine (CRC), R. Engilman (Psychometrician), J. Gold (Psychologist)

University of California, San Francisco Benioff Children's Hospital, San Francisco, CA

P. McQuillen (PI), S. Tabbutt (Sub-I), L. Haeusslein (CRC), S. Strong (CRC), H. Glass (Neurologist), B. Johnson (Psychologist), B. Loomis (Psychologist), D. Gano (Neurologist)

Hospital for Sick Children, Toronto, ON, Canada

J. Hutchison (PI), S. Schwartz (Sub-I), A. Guerguerian (Sub-I), K. Boutis (Sub-I), D. Clark (CRC), J. Van Huyse (CRC), K. Fusco (CRC), K. McBain (CRC), A. Kravecevic (CRC), L. Toller (CRC), R. Gaiteiro (CRC), S. Furness (CRC), R. Askaland (Neurologist), C. Hahn (Neurologist), R. Sananes (Psychologist)

Children's Hospital of Denver, Denver, CO

E. Dobyns (PI), L. Rappaport (Sub-I), E. Jewett (CRC), T. Wilson (CRC), B. Wathen (CRC), M. Dix (CRC), J. Allen (CRC), T. Garling (CRC), D. DiDomenico (CRC), D. Loyola (CRC), T. Bernard (Neurologist), J. Dise-Lewis (Psychologist)

All Children's Hospital, Tampa, FL

A. Stock (PI), K. Battick (CRC), A. Fleming (CRC), J. Hanson (CRC), M. Macogay (CRC), K. Martin (CRC), K. Burger (CRC)

Children's Healthcare of Atlanta, Atlanta, GA

N. Pham (PI), K. Walson (Sub-I), J. Sturm (Sub-I), C. Stone (CRC), A. Wellons (CRC), S. Meisner (CRC), B. Weissman (Neurologist), A. Alexander (Psychologist), A. Johnson (Psychologist)

Anne and Robert Lurie Children's Hospital of Chicago, Chicago, IL

D. Goodman (PI), C. Smith (PI), E. Powell (Sub-I), S. Shah (CRC), J. Chiambrietti (CRC), C. Lutz (CRC), C. Vitt (CRC), L. Jackson-McCarthy (CRC), N. Leannais (CRC), M. Wainwright (Neurologist), J. Goldstein (Neurologist), C. Weil (Psychologist)

Kosair Children's Hospital, University of Louisville, Louisville, KY

M. Porter (PI), J. Sullivan (Sub-I), K. Orman (Sub-I), E. Owen (Sub-I), A. Hardin (Sub-I), K. Potter (Sub-I), E. Peterson (Sub-I), M. Ruppe (Sub – I), J. Berkenbosch (Sub-I), P. Padmanabhan (Sub-I), M. McDonald (Sub-I), V. Montgomery (Sub-I), A. Calhoun (Sub-I), M. Thomas (CRC), A. Michael (CRC), C. Schanie (CRC), L. Rayborn (CRC), K. Kernen (CRC), T. Bratton (CRC), L. Good (CRC), V. Puri (Neurologist), L. Sears (Psychologist)

John's Hopkins Children's Center, Baltimore, MD

U. Bhalala (PI), J. Lee Summers (PI), M. Bembea (PI), D. Shaffner (Sub-I), A. Walker (Sub-I), M. Shackelford (CRC), A. Larson (CRC), J. Jamrogowicz (CRC), J. Kim (CRC), R. Felling (Neurologist), B. Slomine (Psychologist)

Outcome Center, Kennedy Krieger Institute, Baltimore, MD

J.R. Christensen (Site PI), B.S. Slomine (Site Co-Investigator), E. DeMatt (Telephone Interviewer), M. Talley (Telephone Interviewer), C. Rodweller (Telephone Interviewer)

Children's Hospital of Michigan, Detroit, MI

K. Meert (PI), S. Heidemann (Sub-I), J. Clark (Sub-I), A. Pawluszka (CRC), M. Lulic (RA), M. Frey (CRC), L. Sivaswamy (Neurologist), S. Horman (Psychometrician), L. Chiodo (Psychologist)

C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI

F. Moler (PI), R. Stanley (Sub-I), T. Cornell (Sub-I), M. Weber (CRC), J. Reske (CRC), L. Conlin (CRC), F. Silverstein (Neurologist), M. Carlson (Neurologist), S. Warschausky (Psychologist), T. Behnke (Program Administrator), D. Poszywak (Procurement Subcontract Administrator)

Children's Hospital and Clinics of Minnesota, Minneapolis, MN

J. Nowak (PI), H. Ortega (EM Sub-I), D. Milner (EM Sub-I), E. Zielinski (CRC), A. Doucette (CRC), A. Overman (CRC), C. Leonard (CRC), E. Gilles (Neurologist), P. Huszar (Neurologist), M. Troy (Psychologist), J. Alden (Psychologist)

Washington University, St, Louis, MO

J. Pineda (PI), P. Oren (Sub-I), M. Shoykhet (Sub-I), S. Friess (Sub-I), K. Guilliams (Sub-I), D. Jaffe (Sub-I), T. Day (CRC), T. Hicks (CRC), L. Barganier (CRC), E. Fish (CRC), L. Toennies (CRC), P. Thurst (CRC), S. Blankenship (CRC), M. Noetzel (Neurologist), K. Guilliams (Neurologist), D. White (Psychologist).

Children's Hospital of New York/Columbia University Medical Center New York, NY

C. Schleien (PI), J. Cappell (PI), David Schnadower (Sub-I), N. Talathoti (CRC), N. Sidhu (Neurologist), V. Hinton (Psychologist)

University of Rochester Medical Center/Golisano Children's Hospital, Rochester, NY

E. van der Jagt, (PI), E. R. Taillie (CRC), E. Nazarian (Sub-I), L. E. Daugherty (Sub-I), C.O. Davis (Sub-I), J. Mulbury (Neurologist), J. Kwon (Neurologist), H. Adams (Psychologist)

Duke Children's Hospital, Durham, NC

G. Ofori-Amanfo (PI), W. Bordley (Sub-I), S. Wrenn (CRC), T. Uhl (CRC), C. Milleson (CRC), E. Smith (Neurologist), K. Gustafson (Psychologist), S. Asbeck (Psychologist), W. Gallentine (Neurologist)

Nationwide Children's Hospital, Columbus, OH

E. Lloyd (PI), M. Hall (Sub-I), N. Khan (Sub-I), J. Frazier (Sub-I), Daniel Cohen (Sub-I), J. Haines (CRC), K. Carter (CRC), L. Bird (CRC), S. Hough (CRC), W. Lo (Neurologist), K. Yeates (Psychologist), K. Morfing (Psychologist), M. Ginn (Psychologist)

Cincinnati Children's Hospital, Cincinnati, OH

D. Wheeler (PI), G. Geis (Sub-I), E. Beckman (CRC), S. Banschbach (CRC), M. Monaco (CRC), B. Hallinan (Neurologist), N. Walz (Psychologist)

Rainbow Babies and Children's Hospital, Cleveland, OH

K. Lidsky (PI), S. Bergant (CRC), A. Browning (CRC), J. Haky (CRC), N. Bass (Neurologist), R. Tangen (Psychologist)

Penn State Children's Hospital, Hershey, PA

N. Thomas (PI), A. Shelly (CRC), J. Vallati (CRC), P. Carper (CRC), D. Spear (CRC), A. McMonagle (CRC), J. Stokes (CRC), H. Watts (CRC), W. Trescher (Neurologist), C. Flaherty-Craig (Psychologist)

Children's Hospital of Philadelphia, Philadelphia, PA

A. Topjian (PI), R. Berg (Sub-I), V, Nadkarni (Sub-I), S. Friess (Sub-I), J. Fitzgerald (Sub-I), P. Meaney (Sub-I), E. Alpern (EM Sub-I), M. DiLiberto (CRC), C. Twelves (CRC), S. McGowan (CRC), M. Sisko (CRC), B. Park (CRC), R. Ichord (Neurologist), J. Radcliffe (Psychologist), N. Hattiangadi Thomas (Psychologist), K. Friedman (Psychologist), A. Sullivan (Psychometrist)

University of Pittsburgh Medical Center, Pittsburgh, PA

E. Fink (PI), R. Hickey (Sub-I), R. Clark (Planning Committee), M. Bell (Sub-I), A. Abraham (CRC), R. Bell (CRC), R. Varma (Neurologist), S. Beers (Psychologist), H. Feldman (Psychologist), J. Walters (Psychologist), K. McIntyre (Psychologist)

University of Tennessee Health Science Center, Memphis, TN

S. Shah (PI), K. Anand (Sub-I), C. Woodward (Sub-I), A. Hickerson (CRC), B. Moore (CRC), A. Nico West (CRC), M. Grandberry (CRC), N. Shah (Neurologist), N. Clanton (Psychologist), L. Berkelhammer (Psychologist), O. King (Psychologist), A. Huling (Psychologist), L. White (Psychologist)

Children's Medical Center Dallas, University of Texas Southwestern Medical School, Dallas, TX

J. Koch (PI), P. Okada (Sub-I), D. Miles (Sub-I), L. Raman (Sub-I), M. Green (Sub-I), E. Golson (CRC), A. Jones (CRC), D. Kelly (CRC), T. Plumb (CRC), K. Van de Bruinhorst (CRC), M. Dowling (Neurologist), P. Stavinoha (Psychologist), A. Hernandez (Psychometrician)

University of Texas Health Sciences Center at San Antonio, San Antonio, TX

T. Wu (PI), C. Bauerfeld (Sub-I), M. Rodkey (Sub-I), H. Dibrell (CRC), S. Atkinson (Neurologist), L. O'Donnell (Psychologist), J. Eubanks (Psychologist)

Texas Children's Hospital, Houston, TX

L. Loftis (PI), L. Castillo (PI), J. Graf (Sub-I), N. Jaimon (CRC), U. Kyle (CRC), Y. Henry (CRC)

Data Coordinating Center (DCC), University of Utah, Salt Lake City, UT

J. M. Dean (PI), R. Holubkov (Biostatistician), B. Browning (Program Director), M. Gildea (Project Manager), R. Kuhn (Project Manager), K. Register (Project Manager), N. Tattersall (Project Manager), A. Vrem (Project Manager) A. Webster (Biostatistician), A. Clark (Biostatistician), K. Page (Biostatistician), J. Wang (Biostatistician), L. Herrera (Data Manager), J. Yearley (Director Data Management), R. Enriquez (Director Information Technology/Information Systems), D. Demarco (Data Center Manager), M. Virtosu (Senior Software Engineer), S. Su (Senior Software Engineer), J. Bell (Senior Database Developer), S. Zuspan (PECARN Program Director), J. Burr (CPCCRN Program Director), S. Simmons (Information Coordinator), V. McKean (Administrative Assistant), C. Traeden (Administrative Assistant), H. Nitsuma (Administrative Assistant)

Primary Children's Medical Center, Salt Lake City, UT

K.S. Bennett (PI), R. Lane (Sub-I), J. Lilley (CRC), S. Bjerregaard (CRC), K. Jacobsen (CRC), A. Watson, (CRC), D. Stephen (CRC), M. DelaCruz (CRC), K. Cooley (CRC), N. Kwendakwema (CRC), B. Ameel (CRC), G. Jensen (CRC), M. Metcalf (CRC), R. Cole (CRC), R. Moore (CRC), D. Morita (Neurologist), R. Burr (Psychologist), T. Bennett (Sub-I), J. Henricksen (Sub-I), E. Hirshberg (Sub-I), A. Hubbard (Sub-I), G. Larsen (Sub-I), B. Poss (Sub-I), M. Schober (Sub-I), J. Sweney (Sub-I)

Seattle Children's Hospital, Seattle, WA

J. Zimmerman (PI), J. McGuire (Sub-I), R. Farris (Sub-I), O. Yanay (Sub-I), J. Reid (Sub-I), L. Smith (Sub-I), T. Brogan (Sub-I), S. Hamilton (CRC), R. Barker (CRC), C. Greeley (CRC), M. Sadler Greever (CRC), S. Gospe (Neurologist), C. Amlie-Lefond (Neurologist), D. Breiger (Psychologist), A. Paolozzi (Psychologist)

Children's National Medical Center, Washington, DC

J. Berger (PI), D. Wessel (Sub- I), M. Sharron (Sub-I), S. Basu (Sub-I), A. Wratney (Sub-I), N. Dean (Sub-I), K. Brown (Sub-I), J. Reardon (CRC), E. Tomanio (CRC), F. Ramos (RA), B. Tadesse (RA), M. Menicucci (CRC), J. Carpenter (Neurologist), S. Swanson (Psychologist), T. Brennan (Psychologist), P. Glass (Psychologist), B. Malek (Psychologist), M. Mintz (Psychologist)

Medical College of Wisconsin, Milwaukee, WI

M. T. Meyer (PI), M. Wakeham (Sub-I), S. Hanson (Sub-I), Marc Gorelick (Sub-I), M. Christensen (CRC), D. Triscari (CRC), B. Horn (CRC), K. Murkowski (CRC), K. Hecox (Neurologist), C. Brosig (Psychologist)

Clinical Research Networks

Pediatric Emergency Care Applied Research Network (PECARN)

PECARN Steering Committee: P. Dayan, Chair; E. Alpern, L. Bajaj, K. Brown, D. Borgiali, J. Chamberlain, J. M. Dean, M. Gorelick, D. Jaffe, N. Kupperman, M. Kwok, R. Lichenstein, K. Lillis, P. Mahajan, R. Maio, D. Monroe, L. Nigrovic, E. Powell, A. Rogers, R. Ruddy, R. Stanley, M. Tunik

MCHB/EMSC liaisons: D. Kavanaugh, H. Park.

Central Data Management and Coordinating Center (CDMCC): J. M. Dean, H. Gramse, R. Holubkov, A. Donaldson, R. Enriquez, C. Olson, S. Zuspan

Feasibility and Budget Subcommittee (FABS): K. Brown, S. Goldfarb, Co-Chairs; E. Crain, E. Kim, S. Krug, D. Monroe, D. Nelson, M. Berlyant, S. Zuspan

Grants and Publications Subcommittee (GAPS): M. Gorelick, Chair; L. Alpern, J. Anders, D. Borgialli, L. Babcock Cimpello, A. Donaldson, G. Foltin, F. Moler, K. Shreve

Protocol Review and Development Subcommittee (PCRADS): D. Jaffe, Chair; J. Chamberlain, P. Dayan, J.M. Dean, R. Holubkov, L. Nigrovic, E. Powell, K. Shaw, R. Stanley, M. Tunik

Quality Assurance Subcommittee (QAS): K. Lillis, Chair; E. Alessandrini, S. Blumberg, R. Enriquez, R. Lichenstein, P. Mahajan, R. McDuffie, R. Ruddy, B. Thomas, J. Wade

Safety and Regulatory Affairs Subcommittee (SRAS): W. Schalick, J. Hoyle, Co-Chairs; S. Atabaki, K. Call, H. Gramse, M. Kwok, A. Rogers, D. Schnadower, N. Kuppermann

Collaborative Pediatric Critical Care Research Network (CPCCRN)

C.J. Newth, R. Harrison, K. Meert, S. Heidemann, T. Shanley, F. Moler, A. Zuppa, R. Berg, J. Berger, D. Wessel, H. Dalton, M. Pollack, M. Bell, J. Carcillo, A. Donaldson, R. Holubkov,

J.M. Dean, and C. Nicholson for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN).

DSMB

A. Zaritsky, MD (Chair), (Pediatric Critical Care), Eastern Virginia University; Norfolk, VA

A. Atz, MD, (Pediatric Cardiology and Intensive Care), University of South Carolina, Columbia, SC

D. Glidden, PhD, (Biostatistics), University of California San Francisco, San Francisco, CA

J. Lantos, MD, (Bioethics), Children's Mercy Hospitals, Kansas City, MO

M. Gausche-Hill, MD, (Pediatric Emergency Medicine), Harbor-UCLA, Torrance, CA

G. Holmes, MD, (Neurology), Dartmouth University, Hanover, NH

R. Ehrenkranz, MD, (Neonatology), Yale University, New Haven, CT

National Heart, Lung, and Blood Institute, Bethesda, MD

V. Pemberton, J. Kaltman, J. Troendle, G. Pearson

Funding

Primary support for the conduct of the THAPCA-OH Trial was funding from the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute, Bethesda, MD. HL094345 (FWM) and HL094339 (JMD).

Additional support from the following federal planning grants contributed to the planning of the THAPCA Trials: NIH, *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), Bethesda, MD. HD044955 (FWM) and HD050531 (FWM).

In part support was from the participation of the following research networks: Pediatric Emergency Care Applied Research Network (PECARN) from cooperative agreements U03MC00001, U03MC00003, U03MC00006, U03MC00007, and U03MC00008; and the Collaborative Pediatric Critical Care Research Network (CPCCRN) from cooperative agreements (U10HD500009, U10HD050096, U10HD049981, U10HD049945, U10HD049983, U10HD050012 and U01HD049934.

At several centers (indicated above), clinical research support was supplemented by the following grants or Cooperative Agreements: UL1TR000003, P30HD040677, P30HD062171, U07MC09174, UL1 RR 024986, and UL1 TR 000433.

SUPPLEMENTARY METHODS

Inclusion and Exclusion Criteria

Inclusion Criteria (must all be yes)

1. Did the subject suffer a cardiac arrest requiring chest compressions for at least two minutes (120 seconds) with return of spontaneous circulation/return of circulation (ROSC/ROC) for at least 20 minutes?
2. Is the subject greater than 48 hours (with a corrected gestational age of at least 38 weeks) and less than 18 years of age?
3. Does the subject require continuous mechanical ventilation?

Exclusion Criteria (must all be no)

1. Is the parent or legal guardian unable to speak English or Spanish?
2. Is randomization impossible within 6 hours of ROSC/ROC?
3. Does the patient have a Glasgow Coma Scale motor response of 5 or 6 prior to randomization?
4. Did the subject receive continuous infusion of epinephrine or norepinephrine at very high doses (≥ 2 μg/kg/minute) immediately prior to randomization?
5. Does the subject have a history of a prior cardiac arrest with chest compressions for at least 2 minutes during the current hospitalization but outside the 6 hour window for randomization?
6. Does the subject have a pre-existing terminal illness with life expectancy < 12 months?
7. Is there a lack of commitment to aggressive intensive care therapies including “do not resuscitate” orders or other limitations to care?
8. Was the cardiac arrest associated with severe brain, thoracic, or abdominal trauma?
9. Was there active and refractory severe bleeding prior to randomization?
10. Did the subject experience near drowning in ice water with a core temperature ≤ 32 °C on presentation?

11. Is the subject pregnant?
12. Is the patient participating in a concurrent interventional trial whose protocol, in the judgment of the THAPCA investigators, prevents effective application of one or both THAPCA therapeutic treatment arms, or otherwise significantly interferes with carrying out the THAPCA protocol?
13. Is the subject a newborn (< 48 hours of age) with a history of acute birth asphyxia?
14. Was the subject cared for in a neonatal intensive care unit (NICU) after arrest (i.e., would not be admitted to PICU)?
15. Is the subject known to have sickle cell anemia?
16. Is the subject known to have pre-existing cryoglobulinemia?
17. Does the subject have a central nervous system tumor with ongoing chemotherapy or radiation therapy?
18. Does the subject have chronic hypothermia secondary to hypovolemic, pituitary, or related condition for which body temperature is consistently below 37˚C?
19. Does the subject have progressive degenerative encephalopathy?
20. Does the subject have any condition in which direct skin surface cooling would be contraindicated, such as large burns, decubitus ulcers, cellulitis, or other conditions with disrupted skin integrity? (NOTE: subjects with open chest CPR should be included but placement of cooling mattresses will be modified as needed).
21. Has the subject been previously enrolled in the THAPCA Trials?

Site Training

A three day study training meeting was conducted prior to the start of THAPCA-OH Trial. This meeting was repeated annually as a mandatory three day retraining during the conduct of the trial. Additionally, the site neuropsychologists and neurologists received webinar training about the onsite evaluation procedures prior to the first examinations at each site or when there was a change in the site neuropsychologist or neurologist. Training was provided between meetings by one-on-one education sessions with the DCC, webinars and through the use of an online learning management system.

Outcome Training

Baseline Assessment

Caregivers were asked to complete the Parent/Caregiver Rating Form of the VABS-II which is a caregiver questionnaire. Caregivers were asked to base responses on the child's functioning prior to arrest. A site clinical research coordinator or other study staff sat with the family and obtained this information as soon as possible after randomization. If the family was unable to complete the VABS-II within the first 12 hours of admission, the study team tried to obtain the VABS-II every 6 hours until it was completed. Every effort was made to ensure that the VABS-II was completed within 12 hours of randomization. In addition, caregivers provided demographic information, ratings of family functioning, indicators of severity of functioning prior to arrest (e.g., does the child have a tracheostomy tube, ventilator, and/or feeding tube), rating of the child's global functioning, and perceived family burden. At the baseline assessment, information about pre-existing medical conditions and developmental disability was collected and the PCPC/POPC were rated by the study staff based on medical record review.

Early Follow Up

PCPC/POPC ratings were also obtained by the study staff at each site at PICU and hospital discharge.

Three and Twelve Month Follow Up

All 3 and 12 month telephone interviews were conducted centrally by staff at the Kennedy Krieger Institute to assure uniform performance of administration of the semi-structured interview used to collect ratings on the VABS-II. Attempts were made to conduct interviews within one month of the designated follow up time (3 months $\pm$ 2 weeks or 12 months

± 2 weeks). Two to four weeks prior to the telephone interview, site CRCs contacted families to obtain the status of the child and verify current contact information.

In order to assess inter-rater reliability of the VABS-II telephone interviews, a subset of interviews (every 10th interview) was recorded. Recorded interviews were reviewed and rescored by B.S. (neuropsychologist). Discrepant scores were adjudicated through discussion between B.S. and the interviewer. Overall inter-rater reliability was high (> 80% agreement).

During the three and twelve month telephone interview in addition to completing the VABS-II, information about the patient's global functioning, perceived family burden, the patient's medical conditions, as well as school performance (for children 5 years and older) was also obtained. PCPC/POPC ratings were obtained through consensus by J.C. and B.S. (rehabilitation physician and neuropsychologist) based on caregiver responses during the interview.

Twelve Month Onsite Evaluation

After the 12 month VABS-II was completed, onsite neuropsychological and neurological evaluations were completed. All survivors were eligible to participate in the neurological evaluation and all children less than 5 years, 9 months were eligible for participation in the neuropsychological evaluation. Due to limitations in the age range of the tests, children who were 5 years, 9 months through 5 years, 11 months at the time of follow up were tested after their 6th birthday. Children 6 years of age and older who did not have a consistent means of functional communication (based on caregiver responses during the 12 month VABS-II) were not scheduled to participate in the neuropsychological evaluation and were assigned the lowest possible score for purposes of rank order analyses.

As part of the neuropsychological evaluation, a global cognitive score was obtained. For children less than 5 years, 9 months, this score was based on performance on the Mullen Scales of Early Learning (18). In children 6 years of age or older, who were deemed eligible for neuropsychological testing based on the results of the VABS-II, the two subtest version of the Wechsler Abbreviated Scale of Intelligence (19) was used to assess global cognitive functioning.

Data Management and Site Monitoring

Data were recorded on worksheets and entered into a secure Internet-based electronic data capture system (OpenClinica, OpenClinica Inc.) maintained at the DCC (University of Utah, Salt Lake, Utah). Initial VABS-II assessments were faxed to the DCC and centrally scored. Site

monitors visited all enrolling sites to assess protocol adherence, regulatory compliance, and verify sources of selected data elements. This was supplemented by remote monitoring for which sites submitted documentation on selected data elements to the DCC and ongoing automated queries sent to sites for discrepant data.

SUPPLEMENTARY RESULTS

Temperature Intervention.

All temperature recording up to 120 hours were independently reviewed by two individuals (FM and JMD); 92% of TH cases and 90% of TN cases were assessed as Good or Adequate; the remainder were assessed as Poor or Incomplete recordings. Median with interquartile range (IQR) times from intervention initiation to reach goal temperature ranges for at least 1 hour were 2.6 (IQR 1.7, 3.9) for TH and 2.4 (IQR 1.3, 5.0) for TN. For TH cases, the total duration of TH was 48.0 (IQR 48.0, 48.1) hours, duration of rewarming 17.5 (IQR 16.8, 18.0) hours and normothermia after rewarming was 52.0 hours (IQR 50.0, 53.3). For TN cases, the duration was 120 hours (IQR 120.0, 120.1).

Modified Intention-to-treat

While a modified intention-to-treat based on pre arrest VABS-II > 70 score was the primary analysis approach, alternative approaches (modified ITT removing patients not receiving assigned treatment, randomized over 6 hours post ROSC/ROC, and/or otherwise technically not meeting protocol criteria) did not markedly affect significance of study findings or estimated treatment effect. For example, among the 256 evaluable patients receiving their assigned treatment, the p-value for significance of treatment effect was 0.13, and the relative risk for a favorable one-year outcome for patients treated with hypothermia versus normothermia was 1.57 with 95% CI (0.88, 2.80). Among the 246 evaluable patients randomized within 6 hours of ROSC/ROC and receiving their assigned treatment, the p-value for significance of treatment effect was 0.10, and the relative risk for a favorable one-year outcome for patients treated with hypothermia versus normothermia was 1.61 with 95% CI (0.90, 2.87).

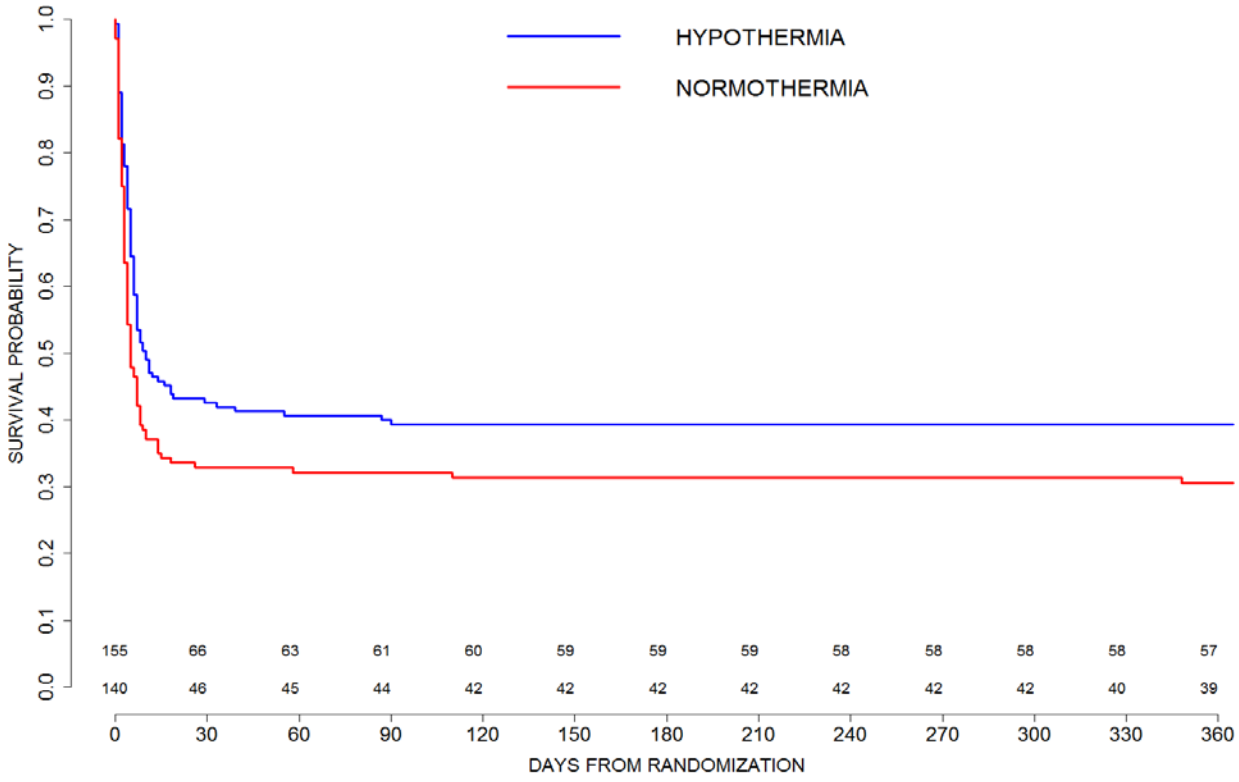
Sensitivity Analysis

Sensitivity analyses were conducted to examine the potential effect of missing primary outcome data on the analysis results. Ten patients eligible for the primary analysis (four assigned to therapeutic hypothermia and six to therapeutic normothermia) had missing outcomes. When all possible realizations of missing outcomes were imputed, the only scenarios yielding significant p-values for treatment effect in the primary analysis occurred when all six children with missing outcome data in the normothermia arm had unfavorable one-year outcomes, and at least three of the four such children in the hypothermia arm had favorable one-year outcomes. Based on

outcomes observed among children with complete data, the chance of such a scenario occurring is estimated to be extremely small. For example, under the observed favorable outcome rates of 19.6% in the therapeutic hypothermia arm and 12.3% in the therapeutic normothermia arm, the estimated binomial probability of such a scenario occurring is less than 1.2%. (Specific characteristics of children with unavailable one-year data also make such scenarios extremely unlikely – for example, one child in the therapeutic normothermia arm with missing primary one-year outcome had a VABS-II score of 103 at three months, and was known to be alive at one year. This child would be considered extremely unlikely to have a poor one-year outcome, as none of the 29 children in the primary analysis with a 3-month VABS-II score of 80 or greater had one-year VABS-II scores below 76.)

SUPPLEMENTARY FIGURES AND TABLES

Figure S1. Probability of survival to one year following cardiac arrest, according to assigned treatment.



The two lines represent Kaplan-Meier survival rates from 0 to 365 days after cardiac arrest for patients in each study arm (p=0.04 for a log-rank test, stratified by age category, comparing survival distributions between treatment arms). Numbers above the *x*-axis represent numbers of patients at risk (alive and followed) in each study arm at each 30-day interval. Restricted mean estimates of survival time, with standard error, are 149 ± 14 days in the Hypothermia group and 119 ± 14 days in the Normothermia group.

Table S1. Clinical Characteristics Prior to Intervention for Study Population.

Clinical characteristics prior to intervention – median (IQR)	**HYPOTHERMIA (N=155)**	**NORMOTHERMIA (N=140)**
First measured body temperature (°C) (n=292)	36.0 (34.2, 37.3)	35.9 (33.8, 37.4)
pH (n=198)	7.20 (7.10, 7.32)	7.24 (7.13, 7.31)
PaCO2 (mmHg) (n=198)	39.5 (34.0, 46.0)	39.0 (32.0, 50.5)
PaO2 (mmHg) (n=197)	98.0 (69.0, 159.0)	104.0 (65.0, 177.5)
Saturation (%) (n=194)	97.0 (89.0, 99.0)	97.0 (91.0, 100.0)
HCO3/Bicarbonate (mmol/L) (n=197)	17.0 (11.0, 21.0)	18.0 (13.0, 21.0)
Lactate (mmol/liter) (n=217)	6.0 (3.2, 10.5)	7.6 (4.0, 11.9)
Sodium (mmol/L) (n=279)	141 (137, 144)	141 (138, 144)
Potassium (mmol/L) (n=278)	3.9 (3.3, 4.6)	4.0 (3.4, 4.8)
Bicarbonate (mmol/L) (n=259)	16.0 (12.0, 19.0)	17.0 (12.0, 21.0)
Chloride (mmol/L) (n=269)	108 (104, 112)	108 (104, 111)
BUN (mg/dL) (n=267)	14.0 (11.0, 17.0)	13.0 (10.0, 17.0)
Creatinine (mg/dL) (n=266)	0.6 (0.5, 0.9)	0.6 (0.4, 0.9)
Glucose (mg/dL) (n=269)	242 (181, 317)	252 (173, 321)
Magnesium (mg/dL) (n=215)	2.3 (2.0, 2.8)	2.4 (2.0, 3.1)
Ionized calcium (mmol/L) (n=234)	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)
Total calcium (mg/dL) (n=223)	8.2 (7.6, 8.7)	8.4 (7.7, 9.0)
Phosphate (mg/dL) (n=192)	5.8 (4.5, 7.8)	6.9 (4.5, 9.6)
ALT/SGPT (U/L) (n=255)	110 (55, 214)	120 (65, 331)
AST/SGOT (U/L) (n=254) *	217 (108, 382)	281 (136, 553)
Total bilirubin (mg/dL) (n=238)	0.3 (0.2, 0.6)	0.3 (0.2, 0.5)
PT (seconds) (n=229)	16.0 (14.1, 18.0)	16.5 (13.9, 19.2)
PTT (seconds) (n=234)	34.0 (28.2, 48.0)	36.0 (30.0, 51.7)
INR (n=237)	1.3 (1.2, 1.5)	1.3 (1.2, 1.7)
Amylase (U/L) (n=152)	61.0 (30.0, 120.5)	97.5 (36.5, 161.0)
Lipase (U/L) (n=152)	86.0 (51.0, 153.0)	82.5 (33.0, 169.0)
Hemoglobin (g/dL) (n=272)	12.4 (11.1, 13.9)	12.1 (10.4, 13.8)
Platelet count (10^3/microL) (n=267)	338 (269, 413)	307 (230, 383)
White blood cell (10^3/microL) (n=266)	14.3 (7.7, 21.1)	15.1 (9.1, 21.3)

* P<0.05 for comparison.

Table S2. Baseline VABS-II, PCPC, and POPC for THAPCA-OH population eligible for primary outcome.

	Hypothermia N = 142	Normothermia N = 128	Overall N = 270
Vineland Adaptive Behavioral Scale-II (VABS-II)			
N (completed and scoreable)	131	115	246
Min	71	70	70
Max	146	141	146
Mean	100.1	102.0	101.0
SD	14	16.3	15.1
Median	100.0	101.0	100.5
Pediatric Cerebral Performance Category (PCPC)			
Normal = 1	128 (90%)	114 (89%)	242 (90%)
Mild disability = 2	11 (8%)	9 (7%)	20 (7%)
Moderate disability = 3	2 (1%)	3 (2%)	5 (2%)
Severe disability = 4	1 (1%)	2 (2%)	3 (1%)
Coma or vegetative state = 5	0 (0%)	0 (0%)	0 (0%)
Pediatric Overall Performance Category (POPC)			
Good = 1	117 (82%)	107 (84%)	224 (83%)
Mild disability = 2	19 (13%)	14 (11%)	33 (12%)
Moderate disability = 3	5 (4%)	4 (3%)	9 (3%)
Severe disability = 4	1 (1%)	3 (2%)	4 (1%)
Coma or vegetative state = 5	0 (0%)	0 (0%)	0 (0%)

Table S3. Cause of Death for patients who died in hospital or within 28 days post-arrest by treatment received.

	Hypothermia N = 88	Normothermia N = 94
Neurologic: brain death declared	34 (39%)	35 (37%)
Withdrawal for poor neurologic prognosis	38 (43%)	39 (41%)
Cardiovascular failure / futility	10 (11%)	12 (13%)
Respiratory failure / futility	2 (2%)	2 (2%)
Withdrawal for other system failure	2 (2%)	2 (2%)
Other	2 (2%)	1 (1%)
Unknown	0 (0%)	3 (3%)

Table S4. 12 month functioning on the Mullen Scales of Early Learning (Mullen) and 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI)[1]

	Hypothermia	Normothermia	P-value
Mullen Early Learning Composite (age < 5 years 9 months) – no. (%)	n=28	n=19	0.97[4]
Lowest possible score[2]	14 (50)	8 (42)	
49 – 69 (well below average)	5 (18)	5 (26)	
70 – 84 (below average)	3 (11)	4 (21)	
85 – 115 (average)	1 (4)	0 (0)	
> 115 (above average)	5 (18)	2 (11)	
WASI IQ (age ≥ 6 years) – no. (%)	n=24	n=16	0.64[5]
Lowest possible score[3]	13 (54)	9 (56)	
55 – 69 (well below average)	2 (8)	3 (19)	
70 – 84 (below average)	2 (8)	2 (13)	
85 – 115 (average)	7 (29)	2 (13)	
> 115 (above average)	0 (0)	0 (0)	
Mullen Early Learning Composite or WASI IQ (all ages combined) – no. (%)	n=52	n=35	0.81[6]
Lowest possible score	27 (52)	17 (49)	
< 70 (well below average)	7 (13)	8 (23)	
70 – 84 (below average)	5 (10)	6 (17)	
85 – 115 (average)	8 (15)	2 (6)	
> 115 (above average)	5 (10)	2 (6)	

[1] Only children alive at one year are represented in table. Nine children, five in the Hypothermia group and four in the Normothermia group, were known to be alive at one year but are not represented because of missing neuropsychological data.

[2] One child in the Hypothermia group with the lowest possible score had this score assigned based on performance during the onsite neurologic evaluation. Specifically, the neurologist indicated that child had no responses to the environment other than pain.

[3] Children age 6 and over with lowest possible score were reported to have no consistent means of functional communication on the 12 month VABS-II assessment interview. These children did not participate in the onsite neuropsychological evaluation and were assigned the lowest possible score.

[4] P-value reflects the Mann-Whitney test based on the continuous Mullen Early Learning Composite score. Patients with a score < 49 are assigned a rank of -1000 (i.e., the lowest possible score).

[5] P-value reflects the Mann-Whitney test based on the continuous WASI IQ score. Patients considered ineligible for the evaluation due to the severity of their injury are assigned a rank of -1000 (i.e., the lowest possible score).

[6] P-value reflects the Mann-Whitney test based on the continuous Mullen Early Learning Composite or WASI IQ score.

Table S5. Adverse Events Reported During Intervention Period (120 hours) by Treatment Received.

	Hypothermia N = 153	Normothermia N = 139	P-value[1]
Hypokalemia[2]	35/153 (23%)	19/139 (14%)	0.04
Hyperkalemia[2]	3/153 (2%)	7/139 (5%)	0.17
Hypoglycemia[2]	12/153 (8%)	12/139 (9%)	0.81
Hyperglycemia[2]	15/153 (10%)	16/139 (12%)	0.64
Hypophosphatemia[2]	7/153 (5%)	6/139 (4%)	0.92
Neutropenia[2]	4/153 (3%)	1/139 (1%)	0.26
Thrombocytopenia[2]	16/153 (10%)	2/139 (1%)	0.001
Clinical or Electrographic Seizure[3]	62/153 (41%)	49/139 (35%)	0.36
Repeat Cardiac Arrest[3]	10/153 (7%)	13/139 (9%)	0.38
Received any form of Renal Replacement Therapy[3]	3/153 (2%)	10/139 (7%)	0.03

[1] P-values for all comparisons are 2-sided mid p-values, based on an exact likelihood ratio test.

[2] MedDRA lower level term of adverse events reported in adverse events log.

[3] Patient experienced event or therapy as reported on daily data collection forms.